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DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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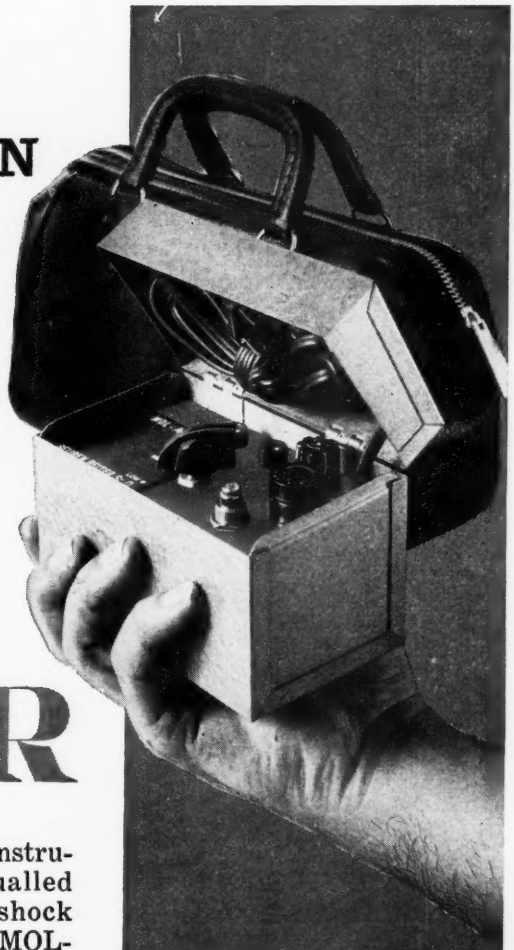

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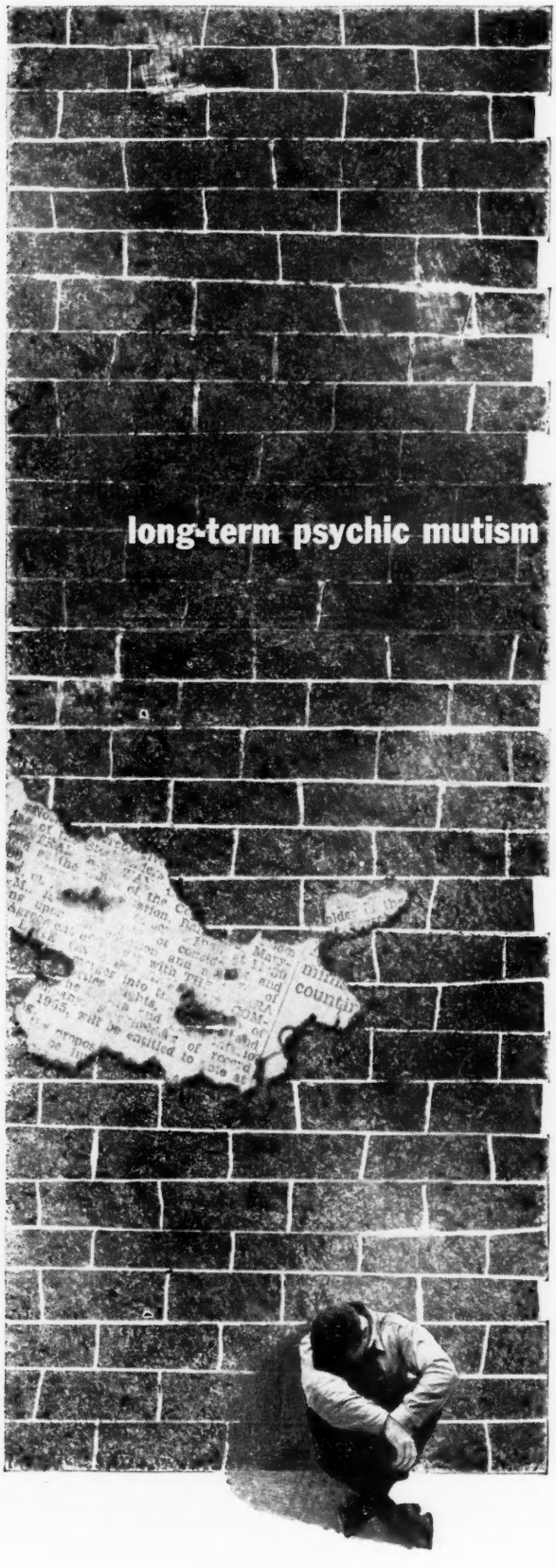

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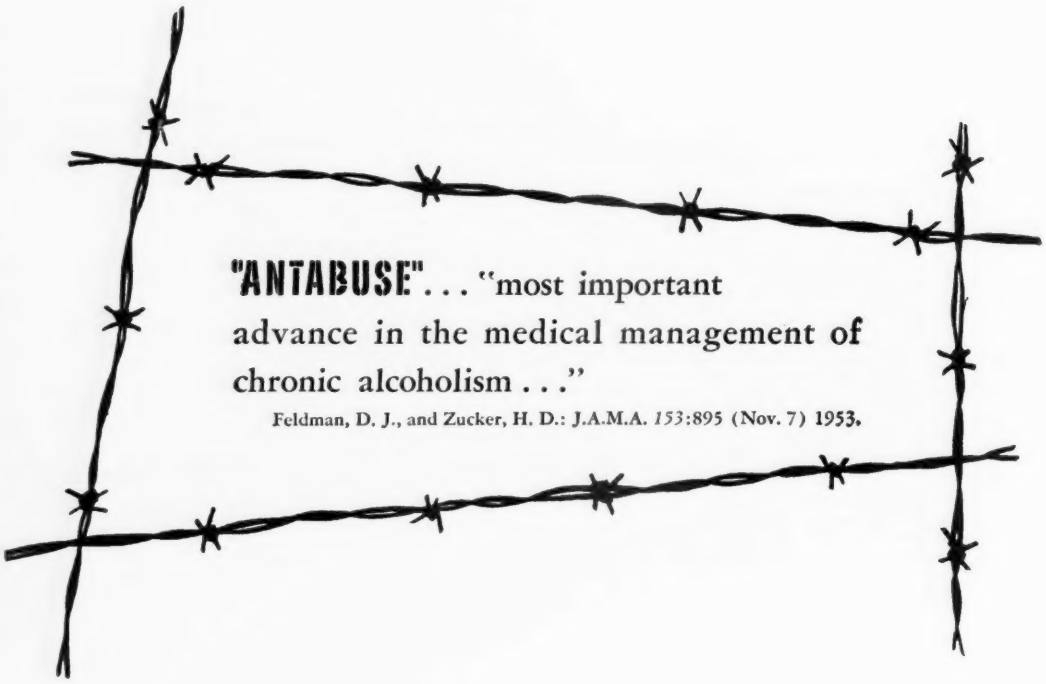
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DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Convulsive Disorders in Medical Diseases

HARRIS MILTON HAUSER
Houston, Texas

Hughlings Jackson postulated the basic mechanism of a convulsion to be the ". . . occasional, sudden, excessive, rapid and local discharge of grey matter," in his definition of epilepsy in 1890. It was not, however, until 1929 when Hans Berger introduced the electroencephalogram into clinical neurology that graphic evidence of this massive discharge of neuronal activity could be definitely shown to contribute to the basic mechanism of the convulsive state. The author intends in this paper to discuss in some detail the mechanism whereby convulsions occur in the various medical diseases; and, further, to summarize and elucidate the recent concepts concerning the common mechanism of the convulsive state.

Because idiopathic epilepsy offers special problems of its own, the discussion to follow will largely be confined to that field of epilepsy most commonly referred to as the "symptomatic epilepsies."

The "symptomatic epilepsies" may be classified in various ways. In Table I they have been grouped together according to certain common biochemical or biophysical mechanisms that they may effect in the pathogenesis of the convulsive state. In any one condition more than one of these pathways may be involved. However, for clarity, pathological conditions have been grouped under that pathway which is believed to be the most important or frequent.

From Baylor Unviversity College of Medicine, Houston, Texas.

Hypoglycemia

Soon after the discovery of insulin in 1921 by Banting and Best, it was noticed that overdosage leading to hypoglycemia frequently resulted in convulsions. Seale Harris[35] in a series of papers on hyperinsulinism and dysinsulinism demonstrated that the hypoglycemia of insulin toxicity is one of the etiological factors in convulsive disorders. Since that time, hypopituitarism and hypoadrenalism (Addison's Disease) have been added to the list of endocrine conditions that may bring about hypoglycemia, and subsequently, convulsions.

Functional hypoglycemia rarely, if ever, is of sufficient severity to precipitate a convulsion. Hyperinsulinism produces hypoglycemia by increasing the passage of glucose across the cell membrane throughout the body at the glucose to glucose-6-phosphate or hexokinase level. This process increases cellular storage subsequently, in the form of glycogen except in the brain. Hyperinsulinism today is seen most frequently following the administration of insulin. Rarely, it is seen with functional adenomas, hyperplasias, or carcinomas of the islet cells of the pancreas.

Normally, the adrenal cortical hormones and anterior pituitary hormones inhibit hexokinase from catalyzing the glucose to glucose-6-phosphate reaction. Insulin is believed to inhibit the action of these two hormones. Thus, in Addison's Disease, where there is a decrease of adrenal cortical hormones, and in hypopituitarism, where there is a decrease

TABLE I

HYPOGLYCEMIA

Hyperinsulinism	(Tumors or Hyperplasia or Islet Cells of Pancreas)
Hypopituitarism	(Acromegaly, Froehlich's Syndrome, Lorraine-Levi Syndrome)
Hypoadrenalism	(Addison's Disease)
Hepatic Insufficiency	(Massive Necrosis of Liver, Hepatotoxins, Von Gierke's Glycogen Storage Disease)

HYPOXIA

Asphyxia

Cerebral Ischemia

- Generalized
  - Adams-Stokes Syndrome
  - Hypersensitive Carotid Sinus Reflex
- Local
  - Meningo-Cerebral Scar (Post-traumatic, Post Infectious)
  - Cerebral Vascular Accidents (Hemorrhage, Thrombosis, Embolism)
  - Peripheral Vascular Disease (Raynaud's Disease, Buerger's Disease)
  - Blood Syscrasias (Polycythemia)
  - Cortical Atrophy (Congenital, Ayzheimer's Disease, Pick's Disease, Porencephalic Cyst)

Cerebral Edema

- Hypertension
- Toxemia of Pregnancy
- Uremia
- Acute Glomerulonephritis
- Protein Shock
- Sudden Increase in Intracranial Pressure
- Toxic Encephalopathies (Exanthems, Serums Injections, Botulinism, Tetanus, Lead)

Tumors

- Neoplastic (Gliomas, Meningiomas, Metastatic Carcinomas)
- Parasitic Cysts (Cystercercosis, Echinoccus Cyst)
- Granulomas
- Abscess

Toxic (e.g. Carbon Monoxide, Cyanide)

Intracranial Inflammations

- Meningitis
- Encephalitis
- Arachnoiditis

INCREASED NEURONAL EXCITABILITY

Alkalosis

- Metabolic (Severe vomiting, excessive ingestion of alkaline salts)
- Respiratory (Hyperventilation, e.g. voluntary, encephalitis, salicylism)

Hypocalcemia

- Tetany of the ewborn
- Hypoparathyroidism
- Nutritional (Dietary deficiencies and severe diarrheal disorders)

Magnesium Deficiency

SUDDEN WITHDRAWAL OF DRUGS IN EPILEPTICS AND NON-EPILEPTICS

Dilantin	Chloral Hydrate	Alcohol
Barbiturates	Paraldehyde	

CONVULSANT DRUGS

Metrazol	Thujone	Anesthetics
Isoniazid	Camphor	Cocaine
Nicotine	Ergot	Asterol
Strychnine	Caffeine	ACTH
Picrotoxin	Epinephrine	Cortisone
Absinth	Prostigmine	

of anterior pituitary hormones, one would expect to find the same hypoglycemia found with increased insulin. There is also a decrease in adrenocorticotrophic hormone secretion in hypopituitarism which leads to a decreased output of adrenal cortical hormones. A second factor that may well be involved here is the decrease of the normal action of adrenal cortical hormones to stimulate the production of glucose from proteins and fats (gluconeogenesis).

Hypoxia

Hypoxia can be brought about by many conditions and represents one of the most frequent basic mechanisms in the pathogenesis of the "symptomatic" convulsion. One of the simplest mechanisms depriving the cells of oxygen is asphyxia due to any process bringing about respiratory obstruction. This mechanism is one of inadequate oxygenation of the blood and a convulsion thus produced is frequently a terminal event if emergency measures are not immediately instituted.

Vascular insufficiency leading to hypoxia may be generalized, but is much more frequently focal. Examples of generalized vascular insufficiency may be found in the Adam-Stokes syndrome in which there is a temporary cessation of cardiac output due to asystole from complete heart block. Another closely related mechanism is that of carotid sinus stimulation, lowering the blood pressure through a decreased cardiac output from excessive reflex vagal stimulation.

In the older age group, one of the more common conditions in which convulsions may arise is the cerebral vascular accident. According to Richardson and Dodge,[68] convulsions will occur in 12.5% of the acute cases. All of the lesions in their series were cortical. Here, the primary mechanism is one of local cerebral ischemia with cellular hypoxia. Another factor which may play a greater or lesser role in the acute case is that of localized edema. Following resolution of the acute insult, a certain percentage of patients will subsequently develop a chronic convulsive disorder. In Richardson and Dodge's series, this was around 5.8%. Here we no longer have a factor of edema. At the periphery of the necrotic area there is scarring and partial restoration of adequate circulation from collateral blood vessels. The neurones in this region are then constantly subjected to a lowered oxygen tension and may constitute a focus for an epileptogenic neuronal discharge.

Probably the most significant mechanism leading to convulsions is that of the meningocerebral scar. According to Penfield and his associates,[61] with scarring of the cortex and the meninges, there is an ingrowth of meningeal vessels. These vessels are supplied by many sympathetic nerve fibres in contradistinction to vessels which supply the cerebral cortex. The neurones present in this scar tissue will be subject to intermittent ischemia leading to hypoxia whenever there is sympathetic stimulation to the ingrowth meningeal vessels. The meningocerebral scar may be a consequence of such lesions as meningitis, encephalitis, cerebral vascular accidents, and traumatic head injury.

Of special interest is the problem of traumatic head injury. Ascroft,[3] in a study of the development of convulsive disorders following gunshot wounds of the head in 317 cases of veterans of World War I, found the development of seizures in 34% of cases at the end of four years. He noted that the incidence of seizures was directly proportional to the depth of penetration; the presence of sepsis; the penetration of the dura, and; the initial period of unconsciousness. His overall incidence was corroborated in studies by Credner[17] and other authors with similar series. The patients in these series had about an 80-85% incidence of skull fracture. Feinberg,[17] in a study of some 47,000 civilian patients (excluding idiopathic and other forms of epilepsy) found an incidence of only 0.1% who subsequently developed convulsions. In his series, there was only an 8% incidence of skull fracture. The incidence in other civilian series was not quite as low as that of Feinberg, being between 2½ to 4½. Those conditions which increased the incidence of seizures in post-traumatic head injuries were conditions which would increase the incidence of development of the meningocerebral scar.

Another major cause of convulsions due to cellular hypoxia is that of expanding intracranial space-occupying lesions. The incidence of convulsions in this group is quite variable. It is highest with the infectious lesions, such as abscesses and parasitic tumors, and least in some of the slower growing non-cortical neoplasms. Here the chief mechanism is probably that of compression of surrounding nervous tissue leading to partial anoxia of the neurones. With rapidly expanding neoplasms and inflammatory lesions, there is certainly an element of interstitial edema in the immediate vicinity of

the tumor which will play a minor or major role in the evolution of the seizure.

The exact mechanism of hypoxia has been questioned recently by the anesthesiologists. Lucus[54] states that the earliest change in anoxic brains is an intracellular edema. Mousel[54] believes that anoxia leads to intracellular edema, which in turn increases cellular anoxia. He obtained good results treating three post-anesthetic encephalopathies with 25% human serum albumin as had been suggested by Seldon et al.[26] A vicious cycle appears to result, therefore, from either anoxia or cerebral edema.

Diffuse cerebral edema without other gross or microscopic abnormalities has been demonstrated in post-mortem examination of brains of patients who died with convulsions. However, in the majority of instances, there have been other demonstrable lesions which indicate that tissue, and consequently, cellular, anoxia have played an etiological role. Murphy,[55] in a discussion of the physiology of intracranial circulation, speaks of the cranial cavity as being a closed system, the pressure of which is maintained by three factors: cerebral blood volume; central nervous system parenchymal volume, and; cerebrospinal fluid volume. When the volume of brain parenchyma is increased as it is in cerebral edema, the volume of one of the two other constituents must be decreased proportionately, thus, cerebral edema may, in addition, affect cerebral blood flow.

Cerebral edema appears to be the primary mechanism of convulsions in protein shock. Sudden increase in intracranial pressure leads to cerebral edema, but also acts similarly to cerebral edema by decreasing cerebral blood flow from increased cerebral vascular resistance. However, Ryder et al.,[72] were unable to demonstrate any change in cerebral function in patients with chronically abnormal cerebrospinal fluid pressure.

The toxic encephalopathies have been found at postmortem examinations to reveal a diffuse cerebral edema when there is no localized encephalitis. The heavy metals, in addition, may have an irritative effect on the surrounding neurones.

Acute glomerulonephritis leads to hypoalbuminemia, decreased plasma osmotic pressure, and consequently, cerebral edema. Hypertension may also be a factor in some cases.

The acute hypertensive encephalopathic crises are usually accompanied by cerebral edema. In addition to the cerebral edema, there is a primary vasospastic element in hypertension which can be visualized in the optic fundi.

Scheinker[55] believes that the hypoxia thus produced leads to dilatation and stasis of the capillary network with diapedesis of plasma and cellular elements, and thus, cerebral edema, as well as the convulsive state. Studies on cerebral circulation have failed to show any marked sympathetic control of intracerebral vessels and further, that the cerebral vessel contractility is regulated primarily by carbon dioxide and oxygen content. Studies by Fazekas et al.,[26] and Shenkin et al.,[77] have demonstrated an increased cerebrovascular resistance in hypertension without arteriosclerosis. This is reversible and is reduced by inhalation of carbon dioxide, and to some degree by thoraco-lumbar sympathectomy.[55] Hypertensive cerebral attacks without edema occur mostly in patients 40-65 years of age with long standing hypertension of severe degree. Angiospasm is assumed to be the cause here. In patients who die during a crisis there is a high incidence of multiple small areas of cerebral infarction.

Eclamptic convulsions are closely related to hypertensive convulsions in their pathogenesis. McCall[11] has demonstrated an increase of cerebrovascular resistance in the toxemias of pregnancy. He has postulated that this is probably due to cerebral edema, increased cerebrospinal fluid pressure, or intracerebral vasospasm. Because of the inconstance of cerebral edema and increased cerebrospinal fluid pressure, he believes vasospasm is the chief mechanism. Holmberg[20] has found multiple areas of encephalomalacia without thrombosis in an eclamptic. Recently Douglas[20] has noted an increase of electroencephalographic abnormalities in prepartum patients without correlation with the subsequent development of toxemia. McIntosh[20] had previously noted abnormal electroencephalograms in 83% of toxemic patients.

Uremia leads to convulsions through several mechanisms. Hypocalcemia is fre-

quently present has been demonstrated to be a cause. However, because of the acidosis which is present, hypocalcemia is an uncommon cause of convulsions. Scheinberg[75] has demonstrated a consistent depression of oxygen and glucose metabolism which does not correlate with the NPN level, mental status, cerebral blood flow, or degree of anemia present. There was an inconstant increase in cerebral blood flow probably related to the anemia.

The exact mechanism or significance of this depression of cerebral metabolism is not yet well understood. Hypertension is felt to account for the convulsions in the majority of the cases.

One of the most interesting facets in the study of the problem of the convulsive state is that of the "febrile" convulsion. This disorder occurs, primarily, in the six to 36 month-old age group in the human, associated with a rapid rise of temperature above normal. Lennox etc.[45,48,49] have estimated that approximately six to seven per cent of all children will have one or more convulsions, the majority of these being febrile. Lennox has been able to produce similar convulsive episodes in kittens but not cats. McQuarrie et al.,[53] were unable to produce convulsions by raising the body temperature with diathermy. They *did* find convulsions with elevation of body temperature due to infection. The only significant metabolic difference noted in these two groups was the decrease in body weight in the diathermy heated patients, whereas there was a slight rise in body weight in the infectious febrile cases. The rise in body weight, as demonstrated by pitressin-hydration studies, was due to the accumulation of body water. Lennox has found an increased incidence of febrile convulsions among acquired epileptics as against the general population. Most investigators have concluded that the febrile convulsion, though not carrying a bad prognostic outlook, is indicative of an inherent lowering of the cerebral threshold to convulsions.

Intracranial inflammations result in many altered conditions which will increase neuronal excitability. The rapid multiplications of pathogens with their high metabolic rate certainly must at least partially deprive the cells of both of their metabolic substrates, oxygen and glucose. There is always an associated localized edema, and frequently, vascular thrombosis. Overman et al.,[59] have demonstrated that the vascular thromboses are due to perivascular proliferation and infiltration. Scheinker[55] believes the vascular thromboses to be the most important altered condition, and has been able to demonstrate their presence at autopsy in a high percentage of cases of encephalitis. Another factor which has been postulated is a direct irritative action of the pathogens on the neurones, and Overman[59] has demonstrated some histological evidence of this. Convulsions, as a late sequel of encephalitis and meningitis, is frequently associated with meningocerebral scars.

The last major group of pathological conditions which may bring about convulsions through hypoxia are certain toxins. This is best exemplified by carbon monoxide poisoning. Carbon monoxide has two hundred times the affinity for hemoglobin that oxygen does. Therefore, with the inhalation of carbon monoxide, the hemoglobin is combined with the carbon monoxide to the exclusion of formation of oxyhemoglobin and the cells suffer as in asphyxia.

Increased Neuronal Excitability

Certain pathological conditions affect the ionic equilibrium of the nerve cells. These conditions, by increasing or decreasing the concentration of the ions in the extracellular fluid, so alter the excitability of the neurone that a lowering of the threshold for rhythmical discharge occurs. In other words, they increase the neuronal state of excitability.

The most common of these conditions is the increase of hydroxyl ion concentration, alkalosis. Alkalosis, or the lowering of the blood pH, is basically brought about under two conditions, respiratory and metabolic.

In respiratory alkalosis, there is lowering of the carbon dioxide content of the blood by the forced blowing off of carbon dioxide through the lungs. This occurs in hyperventilation and encephalitis. The lowering of the carbon dioxide content by this means results in a compensatory decrease in the bicarbonate ion concentration, to maintain the normal bicarbonate ion to carbonic acid con-

centration at a ratio of 20 volumes to 1. This is one of the chief mechanisms by which the blood maintains its pH.

In metabolic alkalosis, the bicarbonate ion of the blood is increased, lowering the carbonic acid to bicarbonate ion ratio, thus elevating the blood pH. This may be brought about by any mechanism lowering the concentration of the acidic ions (such as chlorides in prolonged vomiting) or elevating the concentration of the basic ions (such as sodium in excessive ingestion of sodium bicarbonate). This occurs most frequently in association with renal impairment.

When the pH of the blood is on the alkaline side, dissociation of oxyhemoglobin releasing oxygen to the cell is inhibited. Thus, it may be that some degree of cellular hypoxia also accompanies the abnormal ionic state. Alkalosis has also been shown to decrease the concentration of free calcium ions and thus may produce a state of hypocalcemia.

A decrease in the calcium ion concentration in the extracellular environment similarly increases neuronal excitability. Thus, in conditions leading to hypocalcemia, convulsions are a frequent manifestation. In hypocalcemia there is frequently found at autopsy cerebral edema and increased cerebrospinal fluid pressure. Calcification in the vascular walls of the basal ganglia has been noted, but does not correlate with the occurrence of seizures. Sugar,[8] who recently summarized the literature on the neurological aspects of hypoparathyroidism, believes that the occurrence of seizures is associated with a lowering of the threshold in individuals with an acquired or inherent predisposition to seizures.

Parathyroid hormone regulates the calcium and phosphorus metabolism. It is believed by Reifenstein[36] that its action is to increase the excretion of phosphorus in the urine, which in turn decreases the serum phosphorus level. The decreased ionic phosphorus in the metabolic pool decreases the precipitation of calcium phosphate in bone production. This leads to increased calcium levels in the blood. In hypoparathyroidism the above mechanism works in reverse and the result is a decreased serum calcium.

About 3% of convulsions in the newborn are due to infantile tetany. Bakwin[4] has shown that this represents a "physiological" hypoparathyroidism. Others have suggested that the mechanism might be a decrease of prenatal fetal parathyroid activity. This has been demonstrated in a few cases where the mother was suffering from hyperparathyroidism.

The most common mechanism leading to hypoparathyroidism is removal of the parathyroids during thyroidectomy. Idiopathic hypoparathyroidism is very rare, having an incidence of 1/125,000 cases seen at the Lahey Clinic.[24] Pseudo-hypothyroidism results from failure of the kidney to react to parathyroid hormone stimulation.

Vitamin D increases the absorption of calcium from the gastrointestinal tract, which raises the calcium level in the blood. Therefore when there is decreased calcium in the diet or decreased Vitamin D, there will be decreased absorption of calcium from the gastrointestinal tract. This is not a common cause of convulsions since lowered serum calcium leads to secondary or compensatory hyperparathyroidism, with the clinical picture of bone disorder due to a decrease in the product of calcium times phosphorus. In severe diarrhea, the rapid passage of fluid and metabolites through the gastrointestinal tract does not permit adequate absorption of calcium, and similarly, results in hypocalcemia.

A lowering of the magnesium ion concentration has been found rarely to be responsible for convulsions. Miller[91] in 1944, reported two such cases.

Sudden Withdrawal of Drugs in Epileptic And Non-Epileptic Patients

Pohlish[42] found that the sudden withdrawal of chloral hydrate which had been administered over a long period was associated with seizures. Their incidence associated with the withdrawal of paraldehyde under similar circumstances was even higher. Kalinowsky,[42] in 1942, reported the occurrence of convulsive seizures in seven out of 50-60 non-epileptic mentally disturbed patients who had been under prolonged barbiturate sedation. Two of them had normal electroencephalograms. Status epilepticus, following abrupt discontinuance of phenobarbi-

tal and the hydantoins in epileptics, has frequently been reported. Kalinowsky noted that the delirium following withdrawal of paraldehyde is similar to the delirium tremens found in the chronic alcoholic following the withdrawal of alcohol. Seizures occurring in the so-called "alcoholic" epilepsy or "rum fits" always take place following the withdrawal of alcohol, and the latter, like other anti-convulsants, is primarily a cerebral depressant. Because of the similarity of the delirium following withdrawal of paraldehyde or alcohol, Kalinowsky postulated that alcohol, as well as the other anti-convulsants would not primarily have a convulsant effect, but rather, that their prolonged use as a cerebral depressant was compensated by a lowering of the cerebral threshold for neuronal excitability. Thus, their abrupt discontinuance left the patient relatively more susceptible to convulsions. This hypothesis is further supported by the clinical observation that convulsions do not commonly occur with prolonged alcoholic intake followed by withdrawal in an otherwise normal individual, but is commonly a precipitating factor in the patient predisposed to convulsions (e.g. in idiopathic epilepsy). Bromides, which are also cerebral depressants, are rarely if ever associated with withdrawal convulsions. This is most likely because bromide action requires the replacement of serum ionized chlorides with ionized bromide, there is a prolonged period before the body can rid itself of the bromide ion.

Convulsant Drugs

There are a large number of drugs which have as their primary pharmacological action, or as their side effects, a convulsant action. The majority of these drugs affect cortical and subcortical areas of the brain more than other areas. They represent a heterogeneous group of substances and their mechanisms of action are poorly understood. Metrazol, isoniazid and similar compounds are believed to affect carbonyl trapping and inactivation of amine oxidase within the neurones.

How do these major factors bring about a convulsion? What is the common denominator through which they must act to produce the same end-result? James Collier,[15] in the 1928 Lumlian Lectures on Epilepsy stated: ". . . that clinical phenomenon met with in idiopathic epilepsy, in epilepsy from local lesions of the brain and in the symptomatic epilepsies occurring in disordered metabolic states, in general diseases and intoxications, are identical and are totally indistinguishable . . . and that there is one pathological factor which is common to all of these conditions, and this is hypothesized as a metabolic dyscrasia, the nature of which is not always quite the same, and therefore, different clinical syndromes occur in which the prognosis varies."

The Anatomical Substrate

The anatomical background on which this metabolic dyscrasia acts is complex. From the clinical states discussed above, one can see that the lesions are usually located in the cerebral cortex. Brain tumors, located in the cerebellum, for instance, rarely if ever produce convulsions. This cerebral level corresponds to Hughlings Jackson's highest level of origin of convulsions.

Yakovlev,[90] in a recent paper summarizing his work on the anatomical substrate, discussed the anatomy at three different anatomico-functional levels. The basic level was the conscious or reticulate pattern of neurones which is mainly concerned with background viscero-motor activity. This system, he believes, is responsible for the emotional as well as the autonomic phenomenon in seizures. Through this diffuse system, emotional and other factors act to increase the excitability of the central nervous system, i.e. lower the cerebral threshold for convulsions.

The second anatomical level was the grouping of neurones in nodal patterns (e.g. red nucleus). This level represents the great efferent and afferent patterns of the central nervous system responsible for the rapid conduction of information about the environment to the central nervous system and the rapid conduction of impulses to the efferent sites. It is from this level that we see the motor and sensory manifestations of the seizure.

He defines his third and highest level as the stratilaminate pattern, i.e. the superposition of nerve cell layers as in the cerebral

cortex. This system, he feels, deals with the individual's relationship to his environment, involvement of this system resulting in loss of consciousness.

Gastaut[30] has recently postulated that not only are cortical and subcortical areas involved in convulsions (as Penfield and others have shown), but that the thalamic end of the thalamocortical projections may be of great importance. He believes that the thalamus subserves the purpose of integrating and dispersing impulses from the cortical and sub-cortical level. When there is a localized lesion in, for instance, the precentral gyrus, which gives rise to an epileptic neuronal discharge, the failure of the thalamus to transmit these impulses to other areas of the cortex or to the opposite cortex, productive of loss of consciousness, results in localized Jacksonian seizures. If the thalamus *did* transmit these impulses to the rest of the cortex and throughout the reticulostriate.

The Physiological Substrate

The individual neurones have the function of transmission of an impulse. To this end, they must maintain a state of responsiveness to appropriate stimuli. The state of excitability is an electrical phenomenon depending upon the polarization of the cell membrane. There is an external positive charge and an internal negative charge. Whenever a sufficient area of the cell membrane becomes depolarized, the cell completely discharges, sending an impulse down its axon to the next neurone where, at the synapse, an area of cell membrane will be depolarized, potentially continuing the proportion of the impulse to its effector site.

The maintenance of this state of excitability requires energy derived chiefly from the oxidation of glucose. Some of this energy is utilized to maintain polarization of the cell membrane, and some is used for repolarization. Polarization of the cell membrane is believed to be an ionic state with diffusable potassium ions on the surface held there by the non-diffusable negative charges within the cell. Whenever the potassium ions or the sodium ion concentration in the extracellular fluid is increased, the membrane will depolarize. On the other hand, when concentration of the calcium, magnesium or hydrogen ion is decreased, the cell will also depolarize. Therefore, the excitability of the neurone can be expressed as a constant equal to the ratio

$$\frac{(Ca)\ (Mg)\ (H)}{(K)\ (Na)}$$

The state of normal excitability is dependent upon the maintenance of the concentration of these ions so as to produce a constant value.

The central nervous system is composed of neurones in close approximation to one another and each neurone has a definite effect upon its neighbor. The discharging neurone lowers the threshold for discharge of its neighbor even though there be no direct synapse. If there is a sufficient number of neurones discharging in a small area, excitability of surrounding neurones may be increased to the degree where they too, discharge. This is referred to as recruitment of surrounding neurones and is responsible for part of the massive discharge of neurones during a convulsion. Under normal conditions however, individual neurones discharge asynchronously and may be in a refractory state when surrounding neurones discharge. When the neurones begin to fire synchronously as they do in the above pathological conditions, background for a convulsion exists. Indeed, the neurophysiologists have described the convulsive state as a state of hypersynchrony.

The Biochemical Substrate

The many pathological and physiological factors in the etiology of convulsive disorders have been discussed as have the anatomical and physiological backgrounds, but what is the common lesion which enables all these various conditions to bring about the single common manifestation—a convulsion? Recent work by Tower[82,83,84] has indicated that this common defect is a biochemical one. The mechanism of this lesion is intimately bound up with energy metabolism and functional metabolism at the cellular level.

The two basic substrates necessary for energy production in the brain are glucose and oxygen. Glucose is not stored in the brain and neurones depend upon the circulating glucose level for maintenance of their sup-

ply of carbohydrate. Neurones depend for their energy almost entirely upon carbohydrate metabolism, the brain respiratory quotient being approximately one.

Energy derived from glucose metabolism is stored in the form of rich-energy phosphate bonds produced by the electrification of adenosine to adenosine mono, di, or tri phosphate and is then stored as phosphocreatine. About half of the energy produced by the oxidation of glucose is stored in this manner; the other half is wasted or produces heat. The energy thus produced is utilized to maintain cellular polarization, for repolarization, for transference of glutamic acid across the cell membrane, and in the production of acetylcholine.

Evidence accumulated by many investigators has emphasized the importance of acetylcholine in the convulsive state. Forster[64,82] has shown that acetylcholine will act as a convulsant. Pope et al.,[64,82] have shown a small but significant increase in cholinesterase activity of human focal epileptogenic foci as compared to surrounding and normal tissue. Tower and McEachern[82] found detectable amounts of free acetylcholine in the cerebrospinal fluid of epileptic patients, whereas in most non-epileptic patients, there was none; and that its presence would be correlated with the frequency and occurrence of convulsion in this group. Similarly, many workers have shown that the anticholinesterases act as convulsants. Tower has shown further that cholinesterase activity in epileptogenic foci showed a small increase over the combined non-focal group, and that the production of bound acetylcholine was significantly decreased. He further showed that anesthetics and anticonvulsants, except tridione, increase the ability of normal cerebral cortex to bind acetylcholine.

In this most recent work, he has demonstrated two more defects, a metabolic loss of glutamic acid and a reversal of normal potassium-sodium levels in epileptogenic foci. There was a reduction of glutamic acid levels in epileptogenic tissue after incubation with glutamine which cannot be accounted for by external loss to the surrounding medium and which is not found in non-epileptic tissue. In normal cerebral tissue upon incubation there is an increase in cellular potassium and a decrease in cellular sodium. This is absent or diminished in epileptogenic tissue.

Summary

Long clinical experience has taught that there are varied and seemingly unrelated conditions in which convulsions occur. However, these conditions can be grouped under three basic mechanisms which they may evoke, i.e. hypoglycemia, hypoxia, and increased neuronal excitability. Anatomically and physiologically, there exists in every person the necessary background for a convulsion. These basic mechanisms all lead to several common biochemical lesions. There is a defect in the binding of acetylcholine, a metabolic loss of glutamic acid from the cell and a failure of cellular exchange of sodium for potassium. These lesions implicate a fourth defect, that of ATP.

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Controlled Study on the Value of Chlorpromazine In Allaying Anxiety

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Chlorpromazine has now been used in the treatment of psychiatric disorders for about four years. During this period it has been found to be useful in alleviating a number of symptoms, apparently irrespective of their etiology. Among the symptoms reported as benefited, anxiety and tension figure prominently.[1-8] However, no controlled study on the effect of chlorpromazine has been reported so far. The literature available to date limits itself to describing series of 30 to 150 patients who were given the drug for different symptoms and whose good or bad response is reported and discussed.

In view of the considerable effect of suggestion in psychiatric illnesses, a controlled study in which neither the patients nor the treating staff knew who was getting chlorpromazine and who was receiving placebo tablets seemed indicated. Furthermore, it appeared desirable to evaluate one effect of the medication only in order to increase the accuracy of the ratings. This paper reports the results obtained in the treatment of anxiety in its diverse manifestations with chlorpromazine as compared to identical-appearing placebo tablets. By anxiety we mean the patient's complaining of nervousness, excessive worrying, irritability, uneasiness, sleeping difficulties, and somatic complaints unrelated to physical disease; and showing on examination muscular tension, tremulousness or twitching, restlessness, pressure to relate his difficulties, and autonomic manifestations such as sweating of the palms or flushing of the face.

As a corollary, the patients were also rated on the Multidimensional Scale for Rating Psychiatric Patients devised by M. Lorr[9] in order to obtain an objective index of the change in their over-all clinical status while on the project.

Method

Twenty-one hospitalized psychiatric patients in whom anxiety was a prominent symptom were studied. They were interviewed by three members of the staff before

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and after the course of treatment and evaluated as to the degree of anxiety. This evaluation was recorded by each examiner individually in the form of both a written description and a numerical rating on the following scale: 1.0, normal; 2.0, mildly anxious; 3.0, moderately anxious; 4.0, severely anxious; 5.0 panic state. The averages of these ratings are reported in Tables 1 and 2. In addition, the treating psychiatrist in each case rated the patient on the Lorr Multidimensional Scale for Rating Psychiatric Patients at the beginning and at the conclusion of the trial of therapy.

Nine patients received placebo tablets and twelve received chlorpromazine. The two series were matched as closely as possible with regard to the following criteria: 1. Moderately anxious (3.4 or less), as contrasted to severely anxious (3.5 or more); 2. Length of sickness less than 1 year, as contrasted with more than 1 year; 3. Non-psychotic as contrasted with psychotic; 4. Less than 40 years old, as contrasted with more than 40 years old.

All the patients were white males. Dr. Forsberg matched the patients and decided whether they were to receive chlorpromazine or placebos; he had no other contact with these patients. The hospital pharmacy made up identical bottles for all the patients, identified by the patient's name and prescription number, containing either chlorpromazine (Thorazine) or placebo tablets indistinguishable from Thorazine tablets. Thus, neither the patients nor any member of the staff involved in the management of the patients knew what the patient was receiving. As a precaution, should some unforeseen emergency have arisen, Dr. Fosberg kept envelopes with each of the patients' names on the outside and containing a card stating what the patient was receiving. These were kept in his office, where they were readily available. The need for this safety measure never arose. A white blood cell count and differential count were performed every other week on each patient. The only complications were: 1. Two cases of urticaria (one of them a placebo case); 2. The tremor in a case with paralysis agitans was somewhat increased during the period that he received chlorpromazine.

As the psychiatric service at the Veterans Administration Hospital in New Orleans is an acute treatment service with a small number of beds, patients had to be included in this research project as they were admitted and found suitable. That is why there is not an even number of chlorpromazine and placebo cases.

The patients were started on 50 mg. q.i.d. orally. The dosage was increased by 25 mg. q.i.d. every other day until the desired effect was obtained or until a total of 500 mg. per day was reached. This limit was adopted in view of many reports that cases which benefit at all from chlorpromazine do so at doses of 500 mg. per day or less.[1,4,8] These patients were usually kept on the maximum dose for two weeks before the second rating. A few cases had to be taken off the project after only twelve to fourteen days of treatment due to lack of a favorable response and urgent need of more effective treatment. This appeared to be justified, as it has been our experience in using chlorpromazine that patients who are going to respond favorably to this drug when given orally show some definite improvement during the first 24 to 48 hours after the medication is started.

Each patient was seen by his individual psychiatrist for short sessions, of largely supportive nature, during the course of this study. They were all seen for approximately the same length of time. In addition, they were all assigned to occupational and exercise therapy.

A few of the patients had some organic disease in addition to their psychiatric illness (T is used to designate those patients receiving chlorpromazine (Thorazine), and P is used to designate those patients receiving placebos):

T-1: Paralysis agitans
T-5: Essential vascular hypertension
T-7: Idiopathic epilepsy, grand mal
T-11: Partial deafness
P-4: Venereal warts
P-5: Essential vascular hypertension

These and any other realistic difficulties were taken into consideration in evaluating their anxiety.

Results

The results obtained are summarized in Tables 1-3. On the descriptive evaluations regarding the amount of anxiety manifested by the patients (Table 1) it was the consensus among the members of the staff who examined the patients that eight of the twelve chlorpromazine cases showed a significant decrease in their anxiety, while only two of the nine placebo cases showed a definite decrease in their anxiety.

On the numerical ratings (Table 2) it will be noted that eight of the twelve patients showed an improvement of 1.0 or better as regards their degree of anxiety, whereas only one of the nine placebo cases showed a positive difference greater than 1.0. It is of further interest that the two sets of evaluations coincide except in case of P-7, who was considered improved on the descriptive ratings but improved only 0.7 on the numerical rating.

On the Multidimensional Scale for Rating

TABLE 1.—*Difference Between Initial and Final Descriptive Anxiety Rating.*

	Case No.	Length of Illness	Diagnosis	Age	Anxiety rating difference
Chlorpromazine Cases	T-1	<1 yr.	psychotic	>40	0
	T-2	>1 yr.	psychotic	<40	0
	T-3	<1 yr.	not psychotic	<40	+
	T-4	>1 yr.	psychotic	<40	+
	T-5	>1 yr.	not psychotic	>40	+
	T-6	<1 yr.	psychotic	>40	+
	T-7	>1 yr.	psychotic	<40	+
	T-8	>1 yr.	psychotic	<40	+
	T-9	<1 yr.	not psychotic	<40	+
	T-10	>1 yr.	not psychotic	<40	0
	T-11	<1 yr.	not psychotic	<40	+
	T-12	<1 yr.	psychotic	<40	0
Placebo Cases	P-1	>1 yr.	psychotic	<40	0
	P-2	>1 yr.	psychotic	<40	0
	P-3	>1 yr.	not psychotic	>40	0
	P-4	>1 yr.	psychotic	<40	0
	P-5	>1 yr.	psychotic	<40	0
	P-6	<1 yr.	not psychotic	<40	0
	P-7	<1 yr.	not psychotic	<40	+
	P-8	>1 yr.	not psychotic	<40	+
	P-9	>1 yr.	psychotic	<40	0

+ = significant decrease in anxiety

0 = no decrease in anxiety

TABLE 2.—*Difference Between Initial and Final Numerical Anxiety Rating.*

	Case No.	Initial rating	Final rating	Difference
Chlorpromazine Cases	T-1	4.2	4.2	0.0
	T-2	4.1	4.1	0.0
	T-3	3.8	1.6	+2.2
	T-4	3.8	2.6	+1.2
	T-5	3.4	2.4	+1.0
	T-6	3.2	1.3	+1.9
	T-7	3.2	1.9	+1.3
	T-8	3.2	2.0	+1.2
	T-9	3.1	1.8	+1.3
	T-10	3.0	3.0	0.0
	T-11	2.6	1.1	+1.5
	T-12	2.2	2.7	—0.5
Placebo Cases	P-1	3.8	3.9	—0.1
	P-2	3.8	3.5	+0.3
	P-3	3.4	2.8	+0.6
	P-4	3.0	3.2	—0.2
	P-5	2.7	2.9	—0.2
	P-6	2.6	2.3	+0.3
	P-7	2.6	1.9	+0.7
	P-8	2.5	1.3	+1.2
	P-9	2.2	2.6	—0.4

Average deviation = 0.3.

1.0 = normal; 2.0 = mildly anxious; 3.0 = moderately anxious; 4.0 = severely anxious; 5.0 = panic state.

TABLE 3.—*Difference Between the Initial and Final Morbidity Scores on the MSRPP (Lorr) Scale.*

	Case No.	Initial rating	Final rating	Difference
Chlorpromazine Cases	T-1	29	36	—7
	T-2	28	34	—6
	T-3	25	5	+20
	T-4	44	51	—7
	T-5	26	12	+14
	T-6	19	13	+6
	T-7	26	22	+4
	T-8	38	21	+17
	T-9	16	11	+5
	T-10	17	11	+6
	T-11	33	11	+22
	T-12	18	14	+4
Placebo Cases	P-1	17	15	+2
	P-2	30	19	+11
	P-3	19	24	—5
	P-4	26	28	—2
	P-5	30	38	—8
	P-6	12	17	—5
	P-7	23	11	+12
	P-8	17	11	+6
	P-9	22	20	+2

Standard deviation = 12.1 (according to Lorr)

Psychiatric Patients (Lorr) only four of the twelve chlorpromazine cases and none of the placebo cases improved significantly, that is, more than the stated standard deviation of 12.1 for this scale.

In the patients on chlorpromazine the improvement obtained, both as regards the amount of anxiety and the total clinical status, was unrelated to the patient's diagnosis, age, length of illness, or initial degree of anxiety. On the other hand, the only two placebo cases to improve were diagnosed as nonpsychotic.

The psychotic patients used in this study were either paranoid or hebephrenic schizophrenics or involutional psychotic reactions. The majority were paranoid schizophrenic reactions.

Summary and Conclusions

A "double blind" controlled study on the value of oral chlorpromazine for the symptomatic relief of anxiety and tension is reported. The procedure used to insure that neither the staff nor the patients knew who was a control, and the methods employed for assessing the improvement obtained are described.

It appears from this study that chlorpromazine given orally in doses between 200 and 500 mg. per day is effective in decreasing anxiety in our patients in whom this symptom is prominent. Of the patients benefited by this drug, one-half also appears to improve in over-all clinical status.

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Observations of Speech Disturbances in Childhood Schizophrenia

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Speech disturbances are prominent in the symptomatology of childhood schizophrenia. Mutism, infantile speech, neologisms, substitutions, generalizations, restrictions, disturbances of speaking tone and inflection commonly appear either singly or in various combinations. Personal pronouns are often avoided or reversed.

This paper describes some speech abnormalities observed in schizophrenic children and attempts to correlate these with parental acts and attitudes seen in the concomitant psychotherapy of these children and their parents. The material especially concerns the defensive aspects of the speech of these children.

The Literature. Most theories of schizophrenic speech in adults stress the belief that the ego has given up its object relationships. The individual has lost his desire to communicate and satisfactions must come from within, not from without. The ego is weak and infantile. Freud[1] pointed out that the adult schizophrenic returns to archaic modes of communication; he uses words as substitutes for objects he has given up, thereby partially regaining the lost object.

The child schizophrenic also uses essentially similar mechanisms, but fixation and failure of development, rather than regression, determine the end point. Kanner[2] points out the highly "private" quality of the schizophrenic child's language. Metaphorical expressions (figures of speech that substitute a word or collection of words for what the object only partially resembles) are frequently used, thus producing various substitutes, generalizations, or restrictions of meaning. For example, stags and Indians are considered identical because both are swift. The clarity of expression is distorted in this manner to the point of seeming irrelevance. Kanner emphasises that normal language uses similar mechanisms; for instance, the term "a Don Juan" is commonly used to describe a type of lover. But the metaphors used in schizophrenia differ in that they have no general usage, are highly private, and hence incomprehensible to the ordinary listener. The process provides the individual with greater plasticity, more choices and more chances for wish fulfilment and avoidance of danger, the basis on which Arieti[3] would explain Kanner's metaphoric and private speech. Autistic thought and language "seem to be motivated only or predominantly by an inner or intrapersonal need of the indviidual." The desire for further interpersonal relationships, including communication, is lacking.

Despert[4] also emphasizes the lack of desire for communication, present even though the child may have an extensive vocabulary, and calls it a failure of integration of language-sign and language-function. In her opinion, the avoidance of the use of personal pronouns as well as the disturbances of tone indicate the child's failure to evolve a concept of individuality.

Other clinicians emphasize the defensive aspects of schizophrenic speech in both adults and children. Katan[5] finds that the adult schizophrenic invests the word with the original cathexis of the object and so can more safely express and avoid the danger he fears. Sullivan[6] states that the schizophrenic has given up his hope of satisfaction and is concerned only with his security. In her report of the analysis of a four-year-old schizophrenic, M. Klein[7] speculates that the child's sparse speech, with inability to form symbols and words, was secondary to premature defenses against aggression felt toward the mother. Normally, according to Klein, symbols are formed and used as displacements into the outside world of the original object of aggression, the mother.

The child's language disorder serves as a defense for both child and parent, in my opinion. This process is demonstrated in the material presented from the concomitant psychotherapy of schizophrenic children and

their parents, work which offers a unique opportunity to understand the enmeshing of diseases. One can see the restitutive nature of the symptom. The child has not given up the parent, does not concentrate only on self-satisfaction, but is motivated to preserve a safer relationship with the object. Perhaps the ego in these cases can be described more accurately as paralyzed rather than as simply very weak or stunted.

In considering the parent-child relationship in these cases, one is impressed with the lack of fluidity and communication in the constellation as a whole. In her own way the mother suffers from almost as rigid a freezing of communication as does the child. Clear expressions of feeling, either loving or hostile, are rare. The mother seems unable to conceive of the child as an individual capable of growth, and growth is feared because of its potential destructiveness. The parent-child relationship takes on the character of a prolonged truce between individuals who fear both their affections and their antagonisms. Disarmament and isolation appear as the only practical solutions.

Speech is highly cathected because of its potentiality for the destruction of defenses of both mother and child. The speech pathology represents the resultant of psychological forces in the parent-child relationship, with both parent and child sharing the etiology.

Three cases are given, to illustrate something of my basis for these formulations. The first is presented in more detail, and the other two are summarized briefly.

Case 1. George, a 12-year-old white boy, was hospitalized at the Langley Porter Clinic for three years. The presenting complaints were: complete mutism, present since age 15 months; withdrawal into endless twirling of small objects, such as bottle caps, which he held close to his eyes; and lack of interest in other types of play or in other children.

The patient was born six weeks prematurely, and was kept in the hospital nursery for six weeks. During this period the mother, Mrs. V., could not actually hold and care for him, and she was unable to feel that she was really his mother. When she took him home from the hospital, her first feeling was one of fear that she would drop him. The infant seemed stiff and tense and afraid of the hospital elevator. As soon as they got home, both the father and maternal grandmother insisted on feeding the child, and the mother felt pushed aside, yet unable to resist her mother.

As the grandmother quickly supplanted the mother in actual care of the child, George's mother felt progressively more estranged. The completeness of this psychological separation is illustrated by the mother's inability to hear the infant for his night bottle. When she expressed her pleasure because the child was sleeping through the night, the grandmother acidly commented on her incapacity as a mother, since the child was still waking up and the grandmother was responding and feeding him. Later, when the grandmother left the home for a few months' vacation, the mother immediately was able to hear George cry.

When George was three months old, his mother returned to work, leaving the child's care during the day to baby sitters and the grandmother. Mrs. V. reported that from the beginning she was uncertain about his capacity to develop normally. When he began to walk at 12 months, she was elated. The day after George took his first steps, she took him outside to demonstrate his skills to a friend. He refused to walk and she felt depressed; she was convinced he would not walk normally.

At this time the grandmother left the home for three months. George began to talk, and could say "Mommy" and "Daddy." Mrs. V. reported that this was the happiest time of her marriage, and George seemed happy, too. When the child was 15 months old, Mr. V. entered military service, the beginning of his eventual detachment from mother and child. Mrs. V. became discouraged and more resentful of her mother, who had then returned to the home. At first George seemed to use the word "Daddy" as an epithet and in a few months he stopped talking altogether.

When the boy was four, Mrs. V. began a search for treatment and diagnosis of his condition. Characteristically, the grandmother took the child to various treatment centers, while the mother stayed behind to work, although the father's allotment was enough to support the family. After the father's discharge from military service, he became a merchant seaman and eventually divorced his wife when George was aged 7. The divorce followed years of her husband's promiscuity, about which the wife was fully aware. Although his conduct hurt her and she felt extremely resentful, she was unable to take any firm stand about it before the divorce action. After the divorce, despite her real financial need, the mother was never able to collect the full alimony granted by the court. Late in the course of psychotherapy, she was able to express her feeling that she had no right to her husband's affections or money because she felt so inadequate as a wife and mother.

Psychotherapy was carried out with the mother and child for two years. George, now 9, was seen three times a week in half-hour sessions, and the mother was seen once a week for an hour.

Psychotherapy with the mother revealed her masochism with her mother and husband. This seemed

to serve as a defense against intolerable feelings of personal worthlessness and hostility toward all members of the family. With increasing security in the transference relationship, she first bitterly attacked her mother, then her husband and finally her child. The grandmother was portrayed as an enslaving woman who continued to treat her daughter as an adolescent, demanded to know her whereabouts at all times and refused to recognize any ability for independent action. The patient's rage was ultimately traced to the grandmother's inability to recognize her daughter's need for mothering, and to the patients' fear of mothering because of the danger of personal extinction or incorporation.

For example, she recalled with revulsion being rocked as a child by her mother, but feeling overwhelmed and wishing to escape. Nor could she conceive of a relationship with a father. When she was 5, her father, an alcoholic, was hospitalized for tuberculosis, and upon his discharge 3 years later he deserted the family. He died when she was 10. She greatly resented her mother's defending his desertion and claiming that he was really much interested in all of them. Because of this severe hostility toward both mother and father, she in turn felt unable to relate maternally to her own child.

After expressing these feelings, Mrs. V. began to recognize her own need to repeat with George what she had experienced with her mother. She realized her inability to see him as a boy of 11. She could not conceive of him as a person able to understand what she might say to him. His failure to speak meant that he could not understand her wishes, even though intellectually she knew he did understand what she said.

The mutual stand off in communication between mother and child found devious expressions. With growing self-respect and decreasing fears, Mrs. V. was able to recognize and give up her destructive impulses. She reported an illustrative incident.

The mother's weekly recreation and interest was a game of bowling with friends. Each Friday night she took George home from the hospital, and then left to go bowling. On this particular night George followed her out to the car and indicated his wish to go along. She told him he could not come, and added that children were not allowed in the bowling alleys. He returned to the house. In her interview she expressed much guilt and admitted that her real reason for not allowing him to come was that she was ashamed of his not talking. When I wondered why she had not felt free to be more honest with him, at first she was appalled and then much relieved that I could understand her concern and embarrassment and could believe that George might, too.

She stated that she felt it necessary to maintain many fictions with him. At home both she and her mother talked with George, each answering the other for the child. On holidays her mother sent her a card from George. While alone with the boy she talked to him in a barrage of stereotypes, and he replied in jargon, with the inflection and rhythm of speech. The mother felt incredulous that the boy might direct any spontaneous act toward her. Once George spelled out with blocks the first four letters of his last name. While he was waiting to be praised, the mother ran to get her mother. Upon their return, George destroyed the arrangement. Mrs. V. could not believe that he might be trying to express something to her.

Shortly, after the bowling incident, the mother brought up her fear of hurting George, and reported how she had bitten him in a fit of anger when he was two years old. Having relieved herself of this guilt, she could express her anger at his behavior at home. For example, on weekends he would pull the mattresses from the beds and jump on the bed springs. This behavior had been tolerated for years. Now Mrs. V. became very angry and harshly reprimanded him, saying she would not stand it. He too was angered and ran to his grandmother for help, screaming "Grandmother," and thus abandoning his muteness for the first time in many years, except for an infantile "Bye, bye" on leaving mother. The same weekend George amazed his mother by cutting their lawn, something Mrs. V. thought he was neither interested in nor capable of doing.

George's mother then reported that because of her new-found ability to believe in her own and George's potentiality, he seemed different to her. He felt and looked "more definite." He was observed at home trying to make words while standing before the mirror. He also watched his mother's lips carefully while she spoke. About a year later the child began to speak more regularly.

Case 2. Something of the same process of speech difficulty was observed in another psychotic child. Maria, a 9-year-old girl, was hospitalized 30 months because of urinary soiling, withdrawal, lack of interest in playing with other children, flat and monotonous speech, many phobias of mechanical contraptions, and a bizarre mannerism of waving her hands behind her ears. She used pronouns rarely, avoiding the word "I" and substituting "you" in its stead.

Both parents were seen in concomitant psychotherapy. When the parents, especially the father, were able to recognize and accept their own hostile impulses, they were able to take a firmer stand with Maria. Instead of avoiding the implications of the child's hostile behavior by calling it a symptom of organic brain disease, they held her responsible for her actions. After gaining some mastery of their own hostility, they felt free to expect the same of her, and the child then became able to master some of the routine matters of living. She manipulated door latches and light switches without help and while at home almost entirely stopped soiling herself. Like George's mother, these parents began to see the child as having some personal identity. Her speech began to lose its flat, mechanical quality.

On a weekend just before the child's discharge from the hospital an incident seemed to epitomize

this mutual change. On Sundays Maria used to go to a movie with her grandmother, and each time the parents would ask if she wanted to go. Usually she said no, but because she seemed to enjoy the movie they always sent her. This weekend she again replied that she did not want to go; and when she was being prepared for departure, despite her objections, she asked, "Don't you ever think I want to stay home with you?" The parents could hardly believe such a statement of frank personal commitment, but accepted her wish.

Maria also became more free with other children, especially with her younger sister, who dominated her, but whom Maria always tried to ignore. Now she began to play with the sister and to fight when she felt imposed upon.

Just before her transferral to outpatient status, Maria broached to her mother the coming discharge. She said, "Did you talk to the doctor about going home?" The mother, translating the "you" in its previous usage as meaning Maria, replied, "Did you talk with him?" Maria corrected her with, "I said did you talk with him?" and thereby clearified and accepted her identity.

In this child an interesting exception to the speech disturbance appeared. Maria since infancy had enjoyed a strong attachment to her paternal grandmother, an elderly Italian woman, who spoke a combination of Italian and broken English. Maria regularly talked to her in an animated replica of her grandmother's language. When the parents, attempting to circumvent her usual distortions of communication with them, tried this language, too, she laughed at them and refused to reply.

Case 3. Somewhat closer to the neurotic type of defense in speech is the use of compulsive commands to the ego during speech. The child prevents the expression of over hostility by incorporating the mother's speech into his own. Thus one hears what sounds like two persons talking.

Peter was aged 4½ when he was first brought to the Clinic. He seemed to have little interest in playing with other children and showed evidence of massive withdrawal. His speech was scant, staccato in its delivery and infantile in pronunciation, and the recognizable words were largely a series of commands and prohibitions to himself, spoken in differing pitch and inflection. In the playroom each interest was cautioned against or prohibited with a series of "Don't do that, Peter," or "Get out of there," or "Leave that ball alone." The similarity to certain auditory hallucinations in adults seemed striking.

The struggle for control thus seems to dominate communication. These three cases emphasize the defensive aspects of speech in schizophrenic children. The child's wish appears to be the avoidance of further deterioration of the relationship with love objects. Parents, I believe, unconsciously encourage this solution because they are also fearful of both their own impulses and those of the child.

Other mechanisms may of course help to produce the final distortions that are heard or left mostly unsaid, and each mechanism has its unique dynamic process. Nor is the speech symptomatology devoid of pleasure. The child's inhibitions in communication humiliate and enrage the mother as well as relieve her. "Silence is the most perfect expression of scorn," as Shaw points out.

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A Note on the Alleged Relationship of Trauma to Brain Tumors

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Various types of evidence have been used in court in attempts to prove or disprove the relationship of trauma to the production or aggravation of a brain tumor. The controversy is thoroughly reviewed by Moritz[1] and need not be repeated here. This communication (based on a study of 513 unselected cases of primary intracranial tumor) presents additional proof in this regard.

Undertaken as part of a review of all primary intracranial tumors that have been seen at the University of Texas Medical Branch, Galveston, Texas, from 1892 to 1954, the histories of the cases were reviewed and notation was made of each case in which the patient gave a history of head injury which he thought may have caused his complaints. Since this is the type of case that is most likely to seek compensation in the courts, we wanted to know how many cases of brain tumor gave a history of possibly related trauma.

Furthermore, since Cushing's famous case of General Leonard Wood[2] is so often quoted concerning the relationship of meningiomas to trauma, we wanted to know if certain types of tumor were more likely to be associated with a history of trauma than others. We made no attempt to form opinions concerning the alleged relationship of the trauma to the tumor in individual cases.

The following chart (Fig. 1) shows the findings of this study.

Type of Tumor	Total No. of Cases	History of Head Injury
(Astrocytoma)		
Glioblastoma (Gr. 3 & 4)	167	5
Astrocytoma, grade 1	64	5
Astrocytoma, grade 2	45	3
Medulloblastoma	28	4
Meningioma	77	4
Ependymoma	9	2
Pinealoma	2	1
Pituitary adenoma	26	1
Other types	95	0
TOTAL	513	25

Figure 1. Chart showing the total number of brain tumors and those in which the patient gave a history of head injury which he considered to be related to his complaints.

In none of the following types of brain tumor was there a history of trauma and these cases are included under "other types" in Figure 1: Neurilemoma or neurofibroma 20, oliogodendroglioma 3, glioma unclassified 28, hemangioblastoma 6, angiomas 4, hemangiosarcoma 1, sarcoma of meninges 4, craniopharyngioma 9, colloid cyst of 3rd ventricle 2, epidermoid and dermoid cysts 6, teratomas 1, chordoma of clivus 1, arachnoidal cysts 7, carcinoma of pituitary 2, cyst of pituitary 1 cases.

From these figures it is found that less than one out of twenty cases (4.8%) of primary intracranial tumor gave a history of head injury. The meningioma group does not seem to be related to trauma any oftener than some of the other types, notably the gliomas.

In summary, this study adds additional weight to the evidence against any causal relationship between trauma and primary brain tumors. Only 25 cases, of 513 unselected cases of proved brain tumor, gave a history of a preceding head injury.

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Frenquel

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Our study of the effect of Frenquel in psychotic patients stems from our earlier observance of Meratran[1] and from the work of Howard D. Fabing[2] of Cincinnati in noting the ability of Frenquel to block the development of LSD-25 psychosis. Brown and Werner[3] found that Meratran differed significantly from other central nervous system stimulants, such as the amphetamines. No cardiovascular pressor reactions, no appetite loss, and little disturbance in nocturnal sleep have been observed with this compound, which is useful therapeutically in mild depressive states as well as in narcolepsy and certain selected motor tic syndromes.[4] Himwich and his associates[5] state that Meratran is not a sympathomimetic drug, and they demonstrated that a certain reticular substance of the rabbit brain is stimulated by the compound, followed by cortical stimulation. Heath[6] at Tulane found that Meratran had a unique ability to cause rapid high voltage activity in the septal area of the monkey electrographically.

Because Meratran appeared to act centrally without observable concomitant effects on the autonomic nervous system and because its site of action appeared to be in the upper brain stem tegmentum, it was felt that other compounds of similar clinical configuration might also be of value as therapeutic agents in disorders of the central nervous system. Frenquel is the first of this group of isomers of Meratran to be so utilized.

Frenquel is the gamma-isomer of Meratran. The NH radical is moved from the 2-position to the 4-position in the piperidyl ring in the synthesis of this benzhydrol compound.

Brown[7] has found that Frenquel is different from the parent compound neuropharmacologically. It is not a central excitant but rather, is an antagonist of central stimulation produced by other agents. The early studies of Fabing[2,8] in Cincinnati stimulated us to try the drug clinically. Their first experiments were with healthy graduate students. LSD-25 was ingested to produce a typical psychotic state characterized by hallucinations and delusions. After this initial part of the study the students were started on the blocking agent orally for a week before the LSD-25 was given. When it was ingested, no hallucinations or delusions took place. Similar experiments were carried out on house officers, with similar results, utilizing LSD-25 to produce the psychoses. In addition to this, mescaline produced psychoses have been blocked by Frenquel. One subject was cleared of the symptoms in a matter of minutes by the intravenous administration of Frenquel.

Our studies have been carried out directly on psychotic patients, both in and out of a hospital setting. We attempted no blind experiments, since we believe that suggestion on the part of the physician would have little effect on an acutely disturbed psychotic patient. The patients were not told of the use of a new therapeutic agent. Those who where able to comprehend were simply told: "This is something we want to try to see whether it will help you."

The majority of patients were given complete blood counts, urinalyses, thymol turbidity tests, and blood urea nitrogen studies prior to the beginning of therapy. Some of the patients who have been treated recently have not had these studies, and, of course, patients who were suffering from alcoholic hallucinosis were not tested prior to therapy.

Methods and Results

We have attempted to utilize the medication on patients who symptomatically showed hallucinations of any type, as well as delusions. Unless these symptoms were present,

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Presented before the Southern Psychiatric Association, Atlanta, Georgia, October 4, 1955.

From Bowman Gray School of Medicine, Winston-Salem, N.C.

the treatment was not attempted. The studies were carried out in three groups of patients. One group consisted of 27 patients in a hospital for chronic disorders, giving little more than custodial care and, more recently, reserpine, to the patients. Ten of this group were eliminated from the study because of grossly abnormal laboratory studies. This concerned the administrators of the hospital more than the investigators. The remaining 17 were started on Frenquel, 20 mg. three times a day orally. The results have been poor, as we anticipated. Five of the 17 showed improvement in the symptoms, three marked and two mild. Of the patients who showed the most improvement, two were suffering from marked mental deficiency, with hallucinations and delusions, and the other was suffering from schizophrenia. The remaining 12 patients who showed no improvement ranged from suffering from epileptic deterioration to others suffering from cerebral arteriosclerosis, all having some type of organic psychotic process. Diagnostically, the breakdown was: five with mental deficiency, five with chronic brain syndromes, one with epileptic deterioration, and one with an obsessive-compulsive state, nymphomania, and cerebral arteriosclerosis.

The second group of patients has been treated at Graylyn. This is a 45-bed intensive treatment center operated by the Department of Psychiatry and Neurology of the Bowman Gray School of Medicine and is under the direction of Dr. Lloyd J. Thompson. These patients represented, in the main, more acute psychotic states prior to the onset of deterioration, though some of the latter were included. Here the results in several patients have been gratifying. Again, th same laboratory studies were carried out as in the previous group, though here no patients had to be eliminated because of untoward laboratory results. A total of 35 patients have been under treatment to date. One patient was eliminated from the study because it appeared that after a few days her "paranoid delusions" concerning her husband's infidelity were not delusional, but rather, factual. Patients were started on 20 mg. of Frenquel four times a day, orally, although later, in some, the dosage was changed but without influencing the response. The results revealed 20 patients with marked improvement in their symptoms; six with moderate improvement, and eight with little or no improvement. In the latter group, those who showed little or no improvement, three represented chronic brain syndromes. One suffered from Pick's disease, two from cerebral arteriosclerosis, and two from an exacerbation of previously diagnosed schizophrenia. The patients in the group who showed moderate improvement, or six out of the 34, represented the following diagnostic categories: one, schizophrenia of nine years' duration; one, chronic brain syndrome, and four, depressive reactions with delusions and hallucinations. Moderate improvement indicates that there was a decrease in the delusions and hallucinations of the patient but not complete elimination of them.

In the last group, labeled "marked improvement," the following diagnostic categories were represented: twelve with schizophrenia; one with chronic brain syndrome; one, depressive reaction in a schizoid individual; two, acute unclassified psychotic episode; and four cases of involutional depression. In this group of 20 patients, there was complete alleviation of all hallucinations and delusions except in the patient who had a chronic brain syndrome. She lost her hallucinations completely, but the delusions have persisted, though minimally. These patients ordinarily would have received some form of somatic therapy for their illness. Naturally, with these patients, psychotherapy has been much easier to carry out because of the absence of post-shock confusion, and rapport has been much easier to establish.

The last group of patients comprised 20 with acute toxic hallucinosis. Nineteen had acute alcoholic hallucinosis, and one had hallucinations resulting from bromide intoxication. These patients were seen in the emergency rooms of the two hospitals in Winston-Salem and a few by local internists on home calls. The results obtained in this group of patients have been amazing. In all but three of the patients suffering from delirium tremens there was complete alleviation of symptoms within a matter of hours. The dosage utilized varied a great deal. Frenquel was

given intravenously in doses ranging from 20 mg. to 100 mg. initially. Where lower doses were given, they had to be repeated before complete response was obtained. In some patients the response occurred within thirty minutes, while in others it took three to four hours before maximal results were obtained. The one patient with bromidism responded initially to a dose of 100 mg. intravenously, but within six hours the hallucinations returned. When oral medication was given, the patient again responded within four hours.

Case I: Miss "H," a 22-year-old single white female school teacher, was admitted to Graylyn on April 20, 1955, in an acutely disturbed and psychotic state. Her history revealed that she was well until April 14, six days prior to her admission. She experienced a sudden onset of talking in a bizarre fashion, incessant giggling, ideas of reference, delusions and hallucinations. By April 16, two days after the onset of the illness, she developed the idea that she should get married, that she was pregnant, and, later on, that she was "having a baby." Her examination mentally at the time of admission showed her to be disarrayed, intermittently clutching her abdomen and stating that she was having labor pains. There was overproduction, incoherence, and rambling in her speech. She developed the delusion that she had had intercourse with God and was going to have the son of God. She responded to auditory hallucinations and occasionally to visual hallucinations. She was confined to a disturbed room, and a diagnosis of acute schizophrenic reaction was made. She was given 25 mg. of Frenquel intravenously at the time of admission and was started on Frenquel 20 mg. three times a day orally. On the second hospital day, she was smearing feces all over her body and continued to be agitated and bizarre. In an eflort to control this, we started her on Thorazine, 25 mg. intramuscularly every six hours. On the third hospital day, this was increased to 50 mg. every six hours. She continued to be somewhat hostile and belligerent but was an easier management problem. Three days later she developed a hyperventilation syndrome and some muscular twitchings. All medication except Frenquel was discontinued. Serum chloride, carbon dioxide, total protein, and A.G. ratio were all within normal limits. By April 28, or the eighth hospital day, she was in fairly good contact. She was able to discuss her confusion, expressing some ambivalence about whether or not she had been "off the beam." Her improvement continued. On April 28, she was also started on light doses of insulin to improve her appetite, on which she has continued up until the present time. By the eighth hospital day, she was able to be moved out of the disturbed section, and she has continued to improve since that time. As stated, the insulin has been given in light dosage without any evidence of coma, but the Frenquel has been continued at 20 mg. three times a day. She now shows no evidence of her bizarre ideation, her delusional patterns, or her hallucinations. Psychotherapy has been continued with a satisfying response.

Case II: "John D.," a 46-year-old married white male, was seen in the emergency room of a local Winston-Salem hospital. His family gave a history of his being an alcoholic for twenty years; and he had consumed a fifth of whiskey a day for a week prior to admission. He was acutely intoxicated, disturbed, and had auditory and visual hallucinations. He complained that airplanes were in the room swooping at him and he continually tried to avoid them. He was disoriented as to time and place. He was given Frenquel, 100 mg. intravenously, and within thirty minutes he was calm, oriented, and no longer disturbed. He asked, "What happened to the planes? I thought they were all in the room. Was my mind playing tricks on me?" He was hospitalized for 4 days for massive vitamin therapy, sedatio.., and general medical care, but there was no recurrence of his delusions or hallucinations.

Case III: "Joseph C.," a 39-year-old married white male, was seen at home because of an acute alcoholic hallucinosis. He had been an alcoholic for several year and the week prior to being seen, had consumed large amounts of whiskey. He was confused, disoriented, and complained of seeing animals in the room in the form of spiders, snakes, and rats. He was given 50 mg. of Frenquel intravenously, and within thirty minutes the delusions and hallucinations disappeared. Three hours later, the physician was called to return to the home because of a recurrence of the original symptoms. A second 50 mg. was given intravenously, and again the symptoms disappeared shortly. His family was instructed about giving him fluids, vitamins and sedation, and the original symptoms did not recur.

Conclusions

Frenquel offers a new neuropharmacologic approach to certain acute psychotic states where delusions and hallucinations have been the primary symptoms. In certain selected cases, early results have been encouraging. In patients whose psychoses are associated with organic brain deterioration or chronic brain syndromes, the results have been poor, but we feel that the medication can safely be utilized for a trial of therapy in these patients. We are unable to explain why Frenquel is beneficial in some patients with organic psychoses and not in others. The most encouraging results have been in the treatment of acute toxic hallucinosis, where all but 3 of the patients were relieved of their symptoms withitn a few hours.

We offer this report only as a preliminary one. Further and more intensive studies are being carried out by us. Follow-up studies must be done in these patients before long-term evaluation of the drug can be presented.

Authors' Note: Frenquel is the trade-mark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, for its brand of azacyclonol.

Meratran is the trade-mark of The Wm. S. Merrell Company for its brand of pipadrol.

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Eastern Psychiatric Research Association

This is the name of a newly organized association of psychiatrists, chartered in New York State. The first President is David Impastato, M.D., of New York City. Vice-President is Leo Alexander, M.D., of Boston and Theodore R. Robie, M.D., East Orange, N. J., is Secretary-Treasurer.

The protocol of this new organization's aims and purposes includes the following: "To initiate, encourage and foster research in psychiatry and related fields of medicine . . . to stimulate scientific study and research into the nature and development of human behavior; to organize and coordinate public and private research and efforts in the application of sound principles of psychiatric knowledge . . . to encourage the exchange of scientific knowledge and information in all fields of medicine and especially in the field of psychiatry and mental hygiene."

The Association will hold four meetings per year, including the annual meeting in October. At that meeting, an incentive prize will be awarded for the presentation of the best scientific report.

Members of the Executive Committee are William L. Holt, M.D., Albany, N. Y., Joseph L. Epstein, Katonah, N. Y., Emrich Friedman, M.D., Albany, N. Y., H. B. Lang, M.D., Albany, N. Y.

For information, address Theodore R. Robie, M.D., Secy.-Treas., 676 Park Ave., East Orange, New Jersey. Official transactions will be published in "Diseases of the Nervous System."

Dr. Masserman Returns from Lecture Tour

On November 29th, 1955 Dr. Jules H. Masserman, Professor of Psychiatry and Neurology at Northwestern University, returned from a six-week lecture tour through South America under the auspices of the World Health Organization. During this trip he addressed the faculties of the Universities and various scientific societies at Rio de Janeiro, Sao Paulo, Montevideo, Buenos Aires, Santiago, Lima, Panama, Costa Rica and El Salvador, as well as the psychoanalytic groups in South America. Dr. Masserman will report on the teaching and practice of psychiatry to the World Health Organization and other appropriate agencies.

American Academy of Neurology Sponsors Courses

Special courses in nine different neurological subjects will be presented by a selected faculty at the April 1956 meeting of the American Academy of Neurology in St. Louis, Missouri on April 23, 24 and 25. Three courses will be given daily: Neuropathology, Infectious Diseases in Neurology, Clinical Electroencephalography and Electromyography, Convulsive Disorders, Neurologic Disorders in Infancy and Childhood, Neurochemistry, Injuries to the Nervous System, Current Advances in Neurology. Neurophysiology will require two days. In addition, the Academy will also present a Course for General Practitioners.

For details write Mrs. J. C. McKinley, Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minnesota.

Book Reviews

PSYCHOANALYSIS—PRACTICAL AND RESEARCH ASPECTS by Willi Hoffer, M.D., Ph.D., Editor, The International Journal of Psycho-Analysis. Cloth. $3.50. Pp. 102. William and Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, Maryland. 1955.

In the author's discussion of the function and activity of the therapist in the psychoanalytic setting, he postulates that the criterion of accomplishment is his ability to listen with free floating attention and to follow the patient with a free mind into all the detours which the latter's resistances force him into. It is that free floating attention which is the counterpart to the patient's free associations, and it is the motives which endanger free association that work to endanger free floating attention. The author quite rightly suggests the inability of the therapist to follow patients' material with equal constancy and equal willingness at all times; and it is this human variance in likes and dislikes that, as therapists, we must be ready to both accept and tolerate in ourselves. The author also examines and arrogates to psychoanalytic concern the motivating forces and the methodology of assessment of conflicts which may arise from real or imaginary contradictions between these motivations in human behavior. He characterizes the various approaches in dynamic psychiatry and ascribes them to the differences in technique; and makes the observation that the latter may result in differences in evaluation of the various facets which the conflicts present to the observer. The author contends that much could be said about the influence of child psychiatry upon general psychotherapeutic work with patients of any age, suggests that the problem of adults' difficulties have stimulated a workable approach to child-patient situations and had first induced Freud, with the aid of the child's father, to venture the first psychoanalysis of the phobic little five-year-old Hans. In a later chapter the author presents the history and outlines the course of psychoanalysis of a case of postencephalitic Parkinsonism, with treatment terminated when the organic symptoms of postencephalitic Parkinsonism came to the fore. In his opinion the patient's organic brain changes, as related to inhibitory and release functions, provoked an adaptive reorganization of the patient's personality; and further observed that when organic changes occur unopposed by the psychic personality, ego impoverishment will occur—slowing of movements with rigidity and impediment of voluntary motor control. This ego impoverishment may in turn be compensated by wish fulfillment fantasies of repressed infantile cravings; and by this impedance of the patient's sense of reality he becomes unaware of the changes in his organism. In a discussion of some problems of ego psychology in his final chapter, the author gives expression to the differences in individual instinctive drives and the interplay between them, the ego, and the environment, and stresses the self as a constant in all interchange with one's surroundings. When this constancy is lost, the self, the perception of, and the relationship with the environment suffer disintegration, and psychosis-like states supervene.

The book is clearly written, reflects the author's expressions of wide experience in the therapeutic application of the psychoanalytic aspects of conflict and anxiety, the related topics to child psychiatry, psychological reactions to bodily illness and psychoanalytic appraisal of personality problems of brain diseases—all with illustrative case material. The book may be read with profit by the student of psychoanalysis and by the practitioner irrespective of his particular interest in the discipline of medicine.

Lewis J. Siegal.

ATLAS OF GENERAL SURGERY by Joseph R. Wilder, M.D., Asst. Prof. of Surgery, The New York Medical College, Flower and Fifth Avenue Hospitals. Cloth. $13.50. Pp. 222 with 101 plates. The C. V. Mosby Company, 2307 Washington Blvd., St. Louis, Mo., 1955.

While the atlas embraces within its covers the scope of general surgery and in this connection deals only with one of its components—neurorrhaphy, nevertheless the techniques of each surgical procedure merit favorable comment because of the thoroughness of its portrayal. Of peculiar interest to the neurologist and the psychosomaticist (who frequently see patients after their surgery) is the meticulous description of vital structures involved in each operative procedure depicted. Wherever special nerves or spinal nerves or their trunks traverse the site of the proposed surgical dissection, in addition to the vivid diagrammatic anatomic and photographic illustrations of the various techniques and steps employed (from opening to closure), each surgical plate is preceded by a well written, yet concise dissertation of its every important consideration, and by what to expect to encounter as well as what to avoid when the given condition requires treatment by the surgical route.

PSYCHOSOMATICS by Max Hamilton, M.D., D.P.M., Senior Lecturer, Dept. of Psychiatry, University of Leeds School of Medicine. Cloth. $4.25. Pp. 225. John Wiley & Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1955.

This reviewer shares the author's point of view that although much emphasis has been placed upon attention to the operation of the patient's internal economy after he has been separated from the social environment within which he first became ill, a thorough understanding of psychosomatic illness can only be attained when both the individual's ac-

tion and the reciprocal relationship to his social environment are considered as an entity. Although the author readily adverts to the overwhelming resemblance and correlations between constellations of traits in the various psychosomatic disorders, he maintains his own theory of the different, specific, types of personality for their proneness to their different disorders.

The book accounts for, and quotes by references and dates the many sided theorizations of writers in psychosomatics, includes detailed descriptions of personality disorders, their so-called specific precipitating factors, psychodynamics and mechanisms assigned as producers of particular symptoms and lesions. Impressively, he points out the prevalence of criticism on most of the findings and theories—indicative of the looseness of thought; and adverts to the technical unsatisfactoriness of goodly amounts of published work and of the many contradictions they reveal.

The book is provocative and the author feelingly endeavors to show throughout his scholarly treatise, that classification, in order to stand the test of dependability, must come at the end of a scientific investigation and not at the beginning.

Lewis J. Siegal.

EPILEPSY AND THE FUNCTIONAL ANATOMY OF THE HUMAN BRAIN by Wilder Penfield, O.M., C.M.G., M.D., and Herbert Jasper, M.D., C.M., B.A. Chapter 14 by Francis McNaughton, B.A. and M.D. Cloth. $16.00. Pp. 896 with 8 color plates and 314 black and white illustrations. Little Brown and Company, Boston, Mass., 1954.

The primary objective of the book is its clinical aim toward a better recognition of the operation and interaction as well as causality of epileptic seizures in order to afford a sounder and more efficient approach to treatment of the various patterns of cerebral seizures. From the standpoint of functional neuroanatomy and neurophysiology the authors have elaborately detailed the findings of their electrophysiological research on the activity of the human brain and have vividly demonstrated cortical functional localization during the evolution of the seizure. The results of many studies carried out under local anaesthesis during operative explorations upon focal cortical areas are objectively detailed and microscopic as well as chemical findings from proven seizure-provoking excised cortical tissues reported. The matter of diagnostic manifestations underlying this disturbance in brain function, together with indications for, and principles governing the judicious choice of anticonvulsant drugs as well as a useful description of each of the medicaments named, forms a valuable guide to the conservative treatment of the various forms of epilepsy.

The book is brilliantly written and provides the general practitioner, as well as the specialist concerned with this branch of medicine with an exhaustive text of original scientifically basic and clinical data respecting epileptic seizure—an outward manifestation of an underlying disturbance in brain function.

Lewis J. Siegal.

NEURO-VASCULAR HILA OF LIMB MUSCLES by James Couper Brash, M.C., M.A., D.Sc., LL.D., F.R. C.S., Ed., F.R.S.E., Professor Emeritus of Anatomy, University of Edinburgh. Cloth. $7.00. Pp. 100 with illustrations. The Williams & Wilkins Co., Mount Royal and Guilford Avenues, Baltimore 2, Maryland, 1955.

This 100 page atlas has assembled data on the mode and levels of nerve-entry into the limb muspose is the representation of the extent (percentagepose is the representation of the extent (percentage wise) of the muscular blood supply's correlation with, and the frequency and range of variation with the level of the point of nerve-entry to individual muscles. This area of knowledge is a practical clinical value particularly where electrical methods for diagnosis are used and to determine the treatment of choice in peripheral nerve injuries.

The book is descriptive, is well illustrated with 30 full page plate drawings in color, and should prove of valuable assistance to the neurologist, surgeon and physical therapist.

Lewis J. Siegal

BOOKS RECEIVED

PRINCIPLES OF PUBLIC HEALTH ADMINISTRATION by John J. Hanlon, M.S., M.D., M.P.H. Medical Director, U.S. Public Health Service. Second Edition. Cloth. Pp. 693. The C. V. Mosby Company, 2307 Washington Blvd., St. Louis, Mo., 1955.

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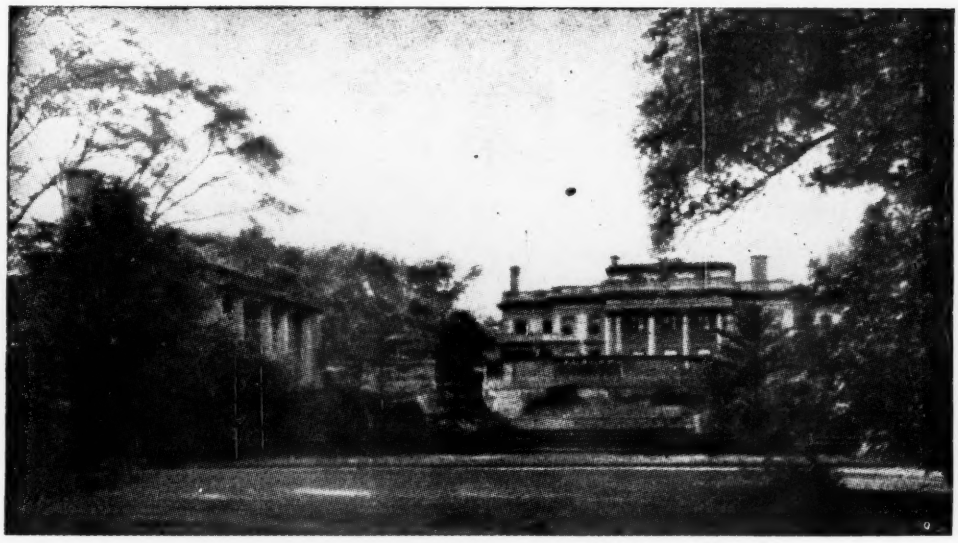
PSYCHOSOMATICS by Max Hamilton, M.D., D.P.M., Senior Lesturer, Dept. of Psychiatry, University of Leeds School of Medicine. Cloth. $4.25. Pp. 225. John Wiley & Sons, Inc., 440 Fourth Avenue, New York 16, N. Y.



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